REMARKS

The Office Action

Claims 1-19 and 51-56 are pending. Claims 1-7, 11-16, and 18 stand rejected for double patenting over claims 1-35 of U.S. Patent No. 7,291,673. Claims 1-19, 51-53, 55, and 56 stand rejected for indefiniteness. Claims 1-19 and 51-53 stand rejected for obviousness over Hubbell et al. (J. Controlled Release, 1996, 39:305-313; hereafter "Hubbell") in view of Harata et al. (Proteins, 1998 30:232-243 and PDB entry; hereafter "Harata") and March (Advanced Organic Chemistry, 4th ed., 1992, pp. 734-770 and 795-797; hereafter "March"). Claim 54 would be allowable if rewritten in independent form.

The Application Is Entitled to Special Status

The present application has been pending for over eight years and has been the subject of seven Office actions. The previous Examiner issued a Notice of Allowance for this application on January 29, 2007. In accordance with their duty of disclosure under 37 C.F.R. § 1.56, Applicants were forced to file a Request for Continued Examination because of the late reporting of an action in the corresponding Canadian application, otherwise the issue fee would have been timely paid.

With respect to previously allowed claims, M.P.E.P. § 706.04 states:

> A claim noted as allowable shall thereafter be rejected only after the proposed rejection has been submitted to the primary examiner for consideration of all the facts and approval of the proposed action.

Great care should be exercised in authorizing such a rejection. See Ex parte Grier, 1923 C.D. 27, 309 O.G. 223 (Comm'r Pat. 1923); Ex parte Hay, 1909 C.D. 18, 139 O.G. 197 (Comm'r Pat. 1909).

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Full faith and credit should be given to the search and action of a previous examiner unless there is a clear error in the previous action or knowledge of other prior art. In general, an examiner should not take an entirely new approach or attempt to reorient the point of view of a previous examiner, or make a new search in the mere hope of finding something. >Amgen, Inc. v. Hoechst Marion Roussel, Inc., 126 F. Supp. 2d 69, 139, 57 USPQ2d 1449, 1499-50 (D. Mass. 2001).< (Emphasis added)

With respect to applications pending for many years and subjected to numerous actions, M.P.E.P. § 707.02 states:

The supervisory patent examiners should impress their assistants with the fact that the shortest path to the final disposition of an application is by finding the best references on the first search and carefully applying them.

The supervisory patent examiners are expected to personally check on the pendency of every application which is up for the third or subsequent Office action with a view to finally concluding its prosecution.

Any application that has been pending five years should be carefully studied by the supervisory patent examiner and every effort should be made to terminate its prosecution. **In order to accomplish this result, the application is to be considered "special" by the examiner**. (Emphasis added)

Finally, Applicants note that three child patents, 6,958,212; 7,291,673; and 7,413,739, have issued since this application was filed.

Given the length of prosecution, the issuance of five non-final Office actions, the previous allowance of all claims, and the issuance of three child applications, Applicants respectfully request that the SPE carefully study this application and make every effort to bring it to final disposition and to treat it as "special," as stated in M.P.E.P. § 707.02.

Rejections for Obviousness-type Double Patenting

Enclosed herewith is a terminal disclaimer to obviate the double patenting rejection over U.S. Patent No. 7,291,673.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-19, 51-53, 55, and 56 stand rejected for indefiniteness. The Office provides two bases for the rejection: (1) the term "functionalized" and (2) the phrase "sensitive biological molecules." As an initial note, the Office has rejected all claims but 54 for indefiniteness; however, the terms to which the Office objects appear only in dependent claim 3 and dependent claim 14. Accordingly, there is no basis for the rejection of claims 1-2, 4-13, 15-19, 51-53, 55, or 56.

In order to advance prosecution and without agreeing with the Office's position, Applicants have now cancelled dependent claims 3 and 14. Independent claims 1 and 5 cover the invention no matter where it is performed and employing any suitable precursor components. This rejection is now moot.

Rejections under 35 U.S.C. § 103

Claims 1-19 and 51-53 stand rejected for obviousness over Hubbell in view of Harata and March. The Office bases this rejection on the theory that one skilled in the art reading the Hubbell reference would desire to produce a composition in which lysozyme

is cross-linked to acrylate containing polymers. The purpose of the Hubbell reference, however, was to incorporate lysozyme in a material non-covalently, and thus, the Hubbell reference provides no incentive for one skilled in the art to produce a composition that is cross-linked using lysozyme as alleged by the Office. Applicants traverse the rejection and provide the enclosed Declaration under 37 C.F.R. § 1.132 by Dr. Hubbell to support the arguments made herein.

As stated by Dr. Hubbell at paragraph 3, "[t]he invention of claim 1 is directed to a method of making a biomaterial using at least two precursors. One precursor includes at least two conjugated unsaturated bonds or groups, and another precursor includes at least two strong nucleophiles. The strong nucleophiles react with the conjugated unsaturated bonds or groups via nucleophilic addition to form the biomaterial."

Dr. Hubbell further characterizes the composition disclosed in the Hubbell reference, which in turn references West et al., Reactive Polymers 1995, 25:139-147 (hereafter "West," copy enclosed), as follows. "[H]ydrogels were formed by the photopolymerization of a single precursor, a diacrylate terminated polyethylene glycol (PEG) co-polymer (West, pg. 141). The purpose of the photopolymerization experiment with proteins was to develop drug delivery vehicles (West, abstract), and the proteins included in the vehicle were not intended to become covalently bound to the hydrogel, as the release mechanism for the protein was diffusion, the rate of which increased as the hydrogel degraded (West, pp. 145-146)."

On this point, the Hubbell reference states:

> The rates of release of proteins of various sizes from a hydrogel utilizing PEG of molecular mass 10 000 Da are shown in Fig. 1 [35]. As expected, small proteins (relative to the permeability of the hydrogel, as determined by the molecular mass of the PEG in the gel) were released by diffusion in the absence of degradation, whereas larger proteins were released by diffusion exclusively following degradation. With this molecular mass PEG chain, this transition between the two regimes occurred somewhere between protein molecular masses of 60 000 and 150 000 Da. Within the regime of release independently of degradation (i.e. molecular mass of 60 000 Da and less), the rate of permeability of the protein through the gel was inversely and linearly related to the molecular mass of the protein. (pg. 311)

According to Dr. Hubbell, the Hubbell reference "indicates clearly that protein incorporated within the PEG diacrylate precursor and resulting PEG-based hydrogel is not covalently incorporated within the gel and does not serve as a crosslinker within the hydrogel material." Accordingly, the Hubbell reference does not teach or suggest "combining two or more precursor components of said biomaterial under conditions that allow polymerization of the components," as required by the instant claims.

Dr. Hubbell further states that the hydrogels of Hubbell and of West are "very different" than the hydrogels of the invention of claim 1. "[I]n the hydrogels of the invention of claim 1, one precursor includes at least two conjugated unsaturated bonds or groups, and another precursor includes at least two strong nucleophiles. In the hydrogels taught in Hubbell and in West, only one precursor is present at all, that containing only unsaturated bonds. These bonds are by nature electrophilic; however, they participate in a free radical reaction rather than an addition reaction. There is no strong nucleophile

present; rather, only the unsaturated groups participate in the gelation reaction." Thus, the Hubbell reference does not teach or suggest a precursor component comprising at least two strong nucleophiles or amines, as required by the present claims.

On the issue of nucleophilic reaction with lysozyme or other proteins described in the Hubbell reference and West, Dr. Hubbell notes at paragraph 4 that the instant specification describes the self-selectivity of this reaction over sensitive biological molecules, e.g., proteins, peptides, and nucleic acids.

> The chemical reaction system of the present invention makes use of addition reactions, in which one component possesses a strong nucleophile and the other component possesses a conjugated unsaturated group, or a conjugated unsaturation. Of particular interest in this invention as strong nucleophiles are thiols. Preferably, the system makes use of conjugate addition reactions between a thiol and a conjugated unsaturation (e.g., an acrylate or a quinone). **This reaction system can be made to be self-selective, meaning substantially unreactive with other chemical groups found in most sensitive biological compounds of interest (most drugs, peptides, proteins, DNA, cells, cell aggregates, and tissues).** It is particularly useful when one or both of these components is part of a polymer or oligomer, however other possibilities are also indicated herein. (Specification, pg. 16, line 22 – pg. 17, line 6; emphasis added)

With particular reference to thiols and amines as nucleophiles, the specification teaches:

> Proteins contain the amino acid cysteine, the side chain of which terminates in a thiol. In spite of this, **there are very few free thiols within the protein: most proteins contain an even number of cysteine residues, and these are then paired and form disulfide cross-links between various regions of the protein. Some proteins contain an odd number of cysteine residues and most of these are present as disulfide linked dimers, again resulting in no free thiol residues being present in the native protein. Thus, there are very few free thiols in proteins.** Some important electron transferring molecules, such as glutathione, contain a free thiol, but these molecules are generally restricted in their spatial

location to the inside of a cell. Accordingly, conjugated unsaturated structures presented outside the cell will be substantially unreactive with most proteins at near-physiological conditions. Amines are also nucleophiles, although not as good a nucleophile as thiols. The pH of the reaction environment is important in this consideration. In particular, unprotonated amines are generally better nucleophiles than protonated amines. **At physiological pH, amines on the side chain of lysine are almost exclusively protonated, and thus not very reactive. The alpha amine of the N-terminus of peptides and proteins has a much lower pK than the side chain epsilon amine; accordingly, at physiological pH it is more reactive to conjugate additions than are the epsilon amines of the lysine side chain.**

Notwithstanding, the thiol is substantially more reactive than the unprotonated amine. As stated, the pH is an important in this consideration: the deprotonated thiol is substantially more reactive than the protonated thiol. In conclusion, the addition reactions involving a conjugated unsaturation, such as an acrylate or a quinone, with a thiol, to convert two precursor components into a biomaterial will often be best carried out (meaning fastest, most self-selective) at a pH of approximately 8, where most of the thiols of interest are deprotonated (and thus more reactive) and where most of the amines of interest are still protonated (and thus less reactive). When a thiol is used as the first component, a conjugate structure that is selective in its reactivity for the thiol relative to amines is highly desirable. (Specification, pg. 17, line 7 – pg. 18, line 8; emphasis added)"

With respect to lysozyme, Dr. Hubbell agrees with the Office at paragraph 6 that lysozyme contains cysteine, lysine, serine, threonine, tyrosine, asparagine, arginine, and glutamine residues. As stated by Dr. Hubbell, however, "[t]he eight cysteine residues in lysozyme form four disulfide bonds. As such, the sulfur atoms in lysozyme are not nucleophilic.... The disulfide bonds would have to be reduced to make the sulfur atoms nucleophilic, and this reduction would result in undesirable destabilization of the

molecule." Based on these properties, Dr. Hubbell concludes, "one skilled in the art would not employ the cysteine residues in lysozyme for covalent attachment to polymers." Dr. Hubbell further notes that "disulfide-reducing conditions were not employed in West, so the lysozyme employed in West did not contain any nucleophilic thiols."

With respect to asparagine and glutamine, Dr. Hubbell also states that the nitrogen atoms in these groups are not nucleophilic as they are both present in an amide group. Similarly, Dr. Hubbell notes that the nitrogen atoms in arginine are also not nucleophilic as they are present in a guanidinium group. In addition, Dr. Hubbell states that the "hydroxyl groups of serine, threonine, and tyrosine are also not strongly nucleophilic, at pH 7.4 in aqueous solution" which are the conditions of the Hubbell and West reactions (West, pg. 141). Finally, Dr. Hubbell states that "the ε-amino group of lysine is not nucleophilic at physiological pH; the α-amino group of a protein is typically somewhat nucleophilic at pH 7.4." And he concludes that under the conditions employed in West, lysozyme has only a single, modestly nucleophilic group at pH 7.4, and lysozyme could not be used to cross-link with another precursor via nucleophilic addition. Again, the Hubbell reference fails to teach or suggest "combining two or more precursor components of said biomaterial under conditions that allow polymerization of the components," as required by the instant claims.

Dr. Hubbell further states that "it is clear from the results presented in West that even strongly nucleophilic groups that are present in proteins mixed within those

materials do not participate in the reaction under the reaction conditions employed in West." Dr. Hubbell notes that in Figure 3 of West (pg. 143), "the protein ovalbumin was released, as shown in the data set denoted with the numeral 4, in a manner that depended only on its molecular weight...." Unlike lysozyme, ovalbumin possesses four unpaired cysteine residues (see, e.g., Huntington and Stein Journal of Chromatography B 2001, 756:189, pg.191, copy enclosed). Dr. Hubbell states: "If these [unpaired cysteine residues] had participated in an addition reaction under the reaction conditions employed in West, and the ovalbumin had become covalently conjugated to the resulting hydrogel, the linear behavior observed in Figure 4 of West (page 144) would not have been observed (the fourth data point from the left)." Dr. Hubbell concludes "even when strong nucleophiles were present under the reaction conditions of West, coupling of protein to the electrophilic end groups on the PEG precursor did not occur." Accordingly, the Hubbell reference fails to teach or suggest any polymerization between a strong nucleophile and a conjugated unsaturated bond or a conjugated unsaturated group, much less the self selective, nucleophilic addition reaction required by the present claims.

In sum, the evidence of record indicates that no lysozyme or other protein is incorporated into a biomaterial via nucleophilic addition under the conditions employed in the Hubbell reference. Furthermore, the purpose of the experiments described in the Hubbell reference was to incorporate proteins non-covalently into a hydrogel made photochemically using a single precursor. Nothing in Harata or March remedies the deficiencies of the Hubbell reference with respect to the instant claims. Accordingly,

there is no reason one skilled in the art would alter the Hubbell reference to produce the present invention, in which two precursor components cross-link via nucleophilic addition. The rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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